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FUNCTION OF CARDIAC MUSCLE

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Translation of "Vliyaniye gipokinezii na sokratitel'nyyu funktsiyu  
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16. Abstract Rats were subjected to hypokinesia for two months and the contractile function of isolated papillary muscle was studied. Hypokinesia reduced significantly the isotonic contraction rate which depended on the ATPase activity of the myofibrils; it also reduced the rate and index of relaxation which depended on the functional capacity of the $Ca^{++}$ -pump of the sarcoplasmic reticulum. The maximum force of isometric contraction determined by the quantity of actomyosin bridges in the myofibrils did not change after hypokinesia. This complex of changes is contrary to that observed in adaptation to exercise when the rate of isotonic contraction and relaxation increases while the force of isometric contraction does not change. The possible mechanism of this stability of the contractile force during adaptation and readaptation of the heart is discussed.			
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## EFFECT OF HYPOKINESIA ON CONTRACTILE FUNCTION OF CARDIAC MUSCLE

by

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It is known that prolonged hypokinesia significantly reduces the resistance of the circulatory system to damaging factors and is one of the main prerequisites for cardiovascular diseases in the modern world. Therefore, the hemodynamics in this state in recent years has been the subject of numerous studies [3,4,8,9]. However, the contractile function of the cardiac muscle during hypokinesia until recently has remained unstudied. Recently, we [8] established that the activity of the heart in animals who were in a state of hypokinesia for a long time was characterized by a decrease by 42% in the rate of pressure development. This shift depended on the reduction in ATP-ase activity of myosin which was also reduced by

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41%. At the same time a considerable deceleration was observed in the rate of pressure drop during the transition from systole to diastole, i.e., decrease in the rate of relaxation of the cardiac muscle. This phenomenon, apparently is governed by a decrease in the functional power of the calcium pump in the sarcoplasmic reticulum of the cardiac muscle cells, which, as is known, ensures the removal of  $\text{Ca}^{2+}$  from the myofibrils and the realization of the process of relaxation.

It is important that depression in the rate of contraction and relaxation was not accompanied in the animals that underwent prolonged hypokinesia by a reduction in the maximum strength of contraction of the myocardium-- maximum pressure developed by the heart with complete short-term pinching of the aorta did not differ from the control amount.

This study left an important question open: is the set of changes in the contractile function found during hypokinesia a result of the change in the spectrum of neurohormonal effects acting on the heart during the experiment, or is it a result of structural changes that developed in the cardiac muscle during prolonged hypokinesia. To solve this problem the given work studied the effect of prolonged hypokinesia on the activity of an isolated papillary muscle whose functional disorders can mainly depend on structural changes that developed in the myocardium during prolonged hypokinesia.

#### Material and Methods

Hypokinesia was induced in Wistar male rats by placing each animal in a separate close box cage for 2 months. As a result the animals lost 25% body weight. The absolute weight of the left cardiac ventricle was not significantly altered, and its relative mass rose by 21%.

Before the beginning of the main experiment the non-narcotized animals were placed in a chamber that restricted their mobility, and with the help of a plethysmographic sensor of the firm "Narco Biosystem" measurements were made of the systolic pressure in the caudal artery and it was recorded together with the EKG on the "Physiograph" instrument of the same firm. /72

EFFECT OF HYPOKINESIA ON INDICES FOR CONTRACTION AND RELAXATION OF ISOLATED MUSCLES ( $M \pm m$ )

Index	Control (n=10)	Hypokinesia (n=10)	% changes	P
load at rest, g/mm <sup>2</sup>				
weight of muscle, mg	0,23±0,02	0,38±0,05	+65	<0,02
length of muscle, mm	5,3±0,8	4,8±0,3	-10	
area of cross section of muscle, mm <sup>2</sup>	3,80±0,15	4,29±0,24	+13	
contraction amplitude, % of initial length	1,39±0,05	1,26±0,08	-10	
time to contraction peak, ms	8,34±1,10	6,21±0,80	-26	
rate of contraction, m. unit/s	110±5,0	110±2,5	0	
rate of relaxation, m. unit/s	1,29±0,17	0,71±0,04	-47	<0,01
index of relaxation, s <sup>-1</sup>	0,86±0,10	0,58±0,04	-33	<0,02
maximum load, g/mm <sup>2</sup>	9,55±0,80	9,41±0,47	-2	
	0,76±0,12	1,11±0,14	+46	

Experiments were conducted on papillary muscles of the left ventricle. The muscle was placed in a chamber with Krebs solution saturated with 95% O<sub>2</sub> and 5% CO<sub>2</sub> at 30°C, and the indices of the isotonic contraction were measured according to the known technique [5] with the help of an isotonic lever, capacitance sensor 51V21 and "Disa" oscilloscope. In the starting period of the experiment the frequency of electrical stimulation was 0.3 Hz. After determining the optimal load at which the contraction amplitude was the maximum, the length of the muscle was recorded. The subsequent increase in the load all the way to the maximum no longer lifted by the muscle made it possible to determine the relationship between the contraction strength and the rate of shortening.

Further the initial rate of stimulation was increased to 1 Hz and on this background the inotropic effect of stimulation was determined by paired impulses with different interval between them, as well as the inotropic effect of increasing the frequency of contractions. The frequency was increased to 2-5 Hz, the duration of the period of increased frequency was 30-40 s, and the interval between them was 5-7 min. At the end of the experiment a study was made of the dynamics of the inotropic effect of noradrenaline (10<sup>-6</sup> M) and decrease in the Ca<sup>2+</sup> concentration in the solution.

In order to compare the results the amplitude of contraction in each experiment was expressed in percentages of the length of the muscle, the rate of contraction and relaxation--in units of muscle length for 1 s

(m. unit/s), load and the amount corresponding to it of the stress developed by the muscle--in grams per  $1 \text{ mm}^2$ . To evaluate the system of relaxation of the myocardium the index of relaxation was determined [5] by dividing the maximum rate of relaxation by the amplitude of contraction.

### Results and Their Discussion

In non-narcotized control rats the frequency of cardiac contractions was  $425 \pm 9$  per minute, while the systolic pressure in the caudal artery-- $109 \pm 2$  mm Hg. Prolonged hypokinesia resulted in an increase in both parameters--the rate of contractions rose to  $477 \pm 10$  per minute, and the pressure--to  $119 \pm 4$  mm Hg. These changes were statistically reliable ( $P < 0.01$  and  $< 0.05$  respectively). The index for intensity of the cardiac contractile function determined by the production of pressure times frequency of contractions was reliably increased by 22%. This shift can be linked to the changed reaction of the animals taken out of close cages to a situation in which the frequency of cardiac contractions and the arterial pressure were measured. At the same time it correlates well with the degree of increase in the relative weight of the left ventricle of the animals, which makes it possible to consider the presence of a certain cause-effect bond between these parameters.

The results of the experiments on isolated papillary muscles are presented in the table; its materials make it possible to isolate three shifts induced by hypokinesia.

The first shift consisted of the fact that the elasticity of the cardiac muscle of animals who were under hypokinetic conditions for a long time was significantly reduced. In fact, for the stretch of muscles to the optimal length at which the maximum strength of contraction was observed, in the control experiments a load of  $0.23 \text{ g/mm}^2$  was required. In experiments on myocardium of animals exposed to prolonged hypokinesia this amount was reliably increased by 65%. Previously it was shown that the increase in this load is combined with the decrease in the elasticity of the myocardium, while the decrease in the load--with an increase in elasticity [1, 2]. Consequently, the reliable increase in the load necessary for stretching of the

cardiac muscle means that hypokinesia resulted in a decrease in the elasticity. This phenomenon is explained with a great percentage of probability by the fact that during prolonged hypokinesia the removal of  $\text{Ca}^{2+}$  from the myofibrils in the sarcoplasmic reticulum is incomplete and in diastole a considerable number of so-called residual actomyosin bridges are preserved [13].

The second shift consisted of the fact that prolonged hypokinesia led to a reduction in the maximum rate of contraction by 47%. It could be thought that this phenomenon depends on the increase in the lifted load which is necessary for stretching the muscle of animals who have undergone prolonged hypokinesia. Therefore to evaluate the real value of this factor from the total number of experiments on papillary muscles of animals exposed to hypokinesia 6 were selected in which the load was the least. As a result it was  $0.26 \pm 0.04 \text{ g/mm}^2$ , i.e., was almost equal to the control amount (see table). However in these experiments the maximum rate and amplitude of contraction were equal respectively to  $0.63 \pm 0.11 \text{ m.unit/s}$  and  $5.36 \pm 1.28\%$ , i.e., were reduced as compared to the control to roughly the same measure as on the whole for the group.

Thus, a decrease in the rate of the isotonic contraction found in our experiments, like the reduction in the maximum rate of pressure development in the experiments *in vivo* [8], apparently is a result of the structural changes that develop during hypokinesia, and first of all, a result of the decrease in ATP-ase activity of the myofibril myosin.

The third shift consisted of the fact that under the influence of hypokinesia the rate of relaxation of the cardiac muscle and the functional power of the membrane mechanisms responsible for  $\text{Ca}^{2+}$  transport were diminished. Thus, the rate of relaxation was reduced by 1/3. In combination with the reduction noted above in the elasticity this can indicate the decline in the ability of the sarcoplasmic reticulum to remove  $\text{Ca}^{2+}$  from the sarcoplasm and myofibrils and realize the process of relaxation. In favor of such an explanation there is the observed change in the inotropic effect of high frequency during prolonged hypokinesia. An increase in the frequency

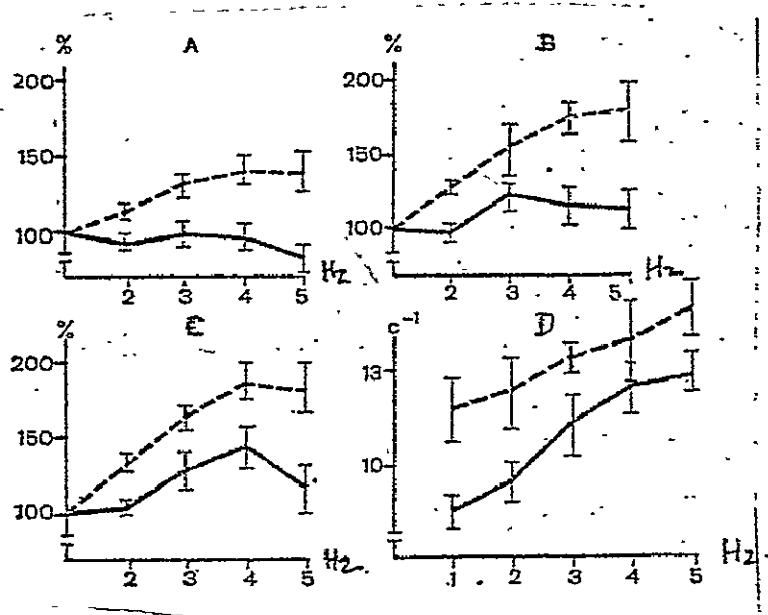


Figure 1. Dynamics of Amplitude of Contraction (A), Rate of Contraction (B), Rate of Relaxation (C) and Index of Relaxation (D) in Short-Term Increase of Contraction Frequency from 1 to 2-5 Hz.

Changes in all the indices with the exception of the index of relaxation are expressed in relative units as compared to the initial amounts with frequency 1 Hz. The upper curves on all figures--control, lower--hypokinesia.

of contractions indices, as is known, an increased influx of  $\text{Ca}^{2+}$  into the myocardial cells and an increase in its entrance into the sarcoplasmic reticulum. As a result, with each subsequent excitation in the myoplasm a larger amount of  $\text{Ca}^{2+}$  enters--a positive inotropic effect of high frequency develops.

Figure 1 shows that the short-term increase in frequency from 1 to 2-5 Hz induces in the control experiments precisely such an effect that is expressed in the increase in amplitude by 40% (see fig. 1,A). In the experiments on papillary muscles of animals who had undergone prolonged hypokinesia the amplitude of contractions in response to the increase in frequency did not rise--the inotropic effect was missing; the increase in rates of contraction and relaxation also was sharply reduced, while the index of relaxation was reliably reduced as compared to the control. The most likely explanation of this fact is that during prolonged hypokinesia

the  $\text{Ca}^{2+}$  activity is reduced of ATP-ase in the sarcoplasmic reticulum responsible for the absorption of  $\text{Ca}^{2+}$  from the sarcoplasm, and therefore additional amounts of  $\text{Ca}^{2+}$  that enter the sarcoplasm with increased frequency are not absorbed by the sarcoplasmic reticulum. The release of  $\text{Ca}^{2+}$  with subsequent excitation does not rise--the inotropic effect is not realized. /74

The reduction in the  $\text{Ca}^{2+}$  fraction that is fed into the sarcoplasmic reticulum apparently has another consequence--increase in the number of  $\text{Ca}^{2+}$  ions absorbed by the mitochondria. An increase in the concentration of  $\text{Ca}^{2+}$  in the mitochondria and in the myocardium as a whole is well known in the compensatory hypertrophy of the heart [17] in which a sharp reduction is observed in the  $\text{Ca}^{2+}$  content in the myocardium [16] and increase in the [5,6] index of relaxation [7]--observed under the influence of adaptation to the physical loads. If under the influence of hypokinesia the entrance of  $\text{Ca}^{2+}$  into the sarcoplasmic reticulum is actually reduced, while the  $\text{Ca}^{2+}$  content rises in the mitochondria, then this must promote an increase in resistance of the contractile function of the myocardium to a  $\text{Ca}^{2+}$  deficit in the medium, since the  $\text{Ca}^{2+}$  accumulated in the mitochondria can be mobilized opportunely.

In fact, in the first minutes after reduction in the  $\text{Ca}^{2+}$  concentration in the solution two-fold, when the amplitude and rate of contraction and relaxation in the control experiments were reduced by 25-30%, the indices for the process of contraction and relaxation of the myocardium of animals exposed to hypokinesia practically were not altered (fig. 2).

These results indicate that during hypokinesia both the rate of use of energy in the myofibrils and their shortening, and the rate with which the sarcoplasmic reticulum absorbs  $\text{Ca}^{2+}$  and realizes relaxation are decreased.

Simultaneously, it follows from the data of the table that the maximum load characterizing the maximum stress developed by the papillary muscle is not altered under the influence of hypokinesia.

It is known that isometric contraction is linked to a considerably greater consumption of ATP and consumption of oxygen than the isotonic contraction [12, 14] with which we have been concerned until now. The /75

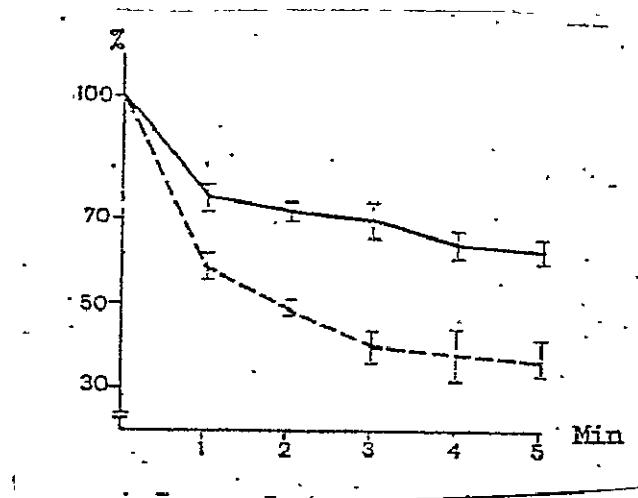


Figure 2. Dynamics of Reduction in Amplitude of Contraction of Myocardium of Control (lower curve) and Animals Who Have Undergone Hypokinesia (upper curve) in First Minutes after Reduction in Concentration of Calcium in Solution from 2.5 to 1.2 mM (M<sub>M</sub>).

All changes between groups are statistically reliable ( $P < 0.01$ ).

absence of a depression in the force of such a contraction means that hypokinesia did not result in any disorder in the system of energy supply in the cells of the cardiac muscle.

It is important that a reduction in ATP-ase activity of myosin under the influence of hypokinesia is combined with the absence of changes in the maximum strength of contractions. Previously it was shown that an increase in ATP-ase activity of myosin under the influence of adaptation to the physical loads [11, 18] is also combined with the absence of changes in the maximum strength of contractions [7]. This set of facts is explained, in our opinion, by the fact that in isometric contraction the role of ATP-ase of myosin that determines the rate of formation and elimination of actomyosin bridges is relatively small, since the active centers of actin and myosin protofibrils for a long time oppose each other in the stressed, but not in the shortening muscle. The maximum strength developed here by the muscle is determined by the maximum number of actinomyosin bridges that can be formed in a unit of volume of the muscle with sufficient influx of ATP to the myofibrils. The myofibril is a stable structural formation in which the active centers in the actin and myosin protofibrils are arranged

in strictly determined sections roughly in  $400 \text{ \AA}$  from each other, their number is genetically determined, and apparently cannot be altered under the influence of such "transient" situations of individual life as deadaptation or adaptation, hypertrophy or atrophy of the muscle cells.

In contrast to this the rates of isotonic contraction and relaxation under the influence of hypokinesia are reduced, and under the influence of adaptation to the physical loads rise, probably as a consequence of the increase in ATP-ase activity of myosin and the maximum functional power of the calcium pump of the sarcoplasmic reticulum [15]. Thus, the idea is noted that during adaptation and deadaptation the structural shifts in the cardiac muscle cells result in changes in the rate of emergence and elimination of the actomyosin bridges, and at the same time in a change in the rate of contraction and relaxation. The total number of actin and myosin centers and the maximum number of actomyosin bridges here, probably are not altered, correspondingly the maximum stress of the cardiac muscle also remains unchanged. It is likely that in principle such variants of adaptation and deadaptation are possible in which an increase or decrease occurs in the concentration of contractile proteins and the number of myofibrils per unit of cell volume. In such cases, apparently, the number of actomyosin bridges can be altered and the maximum stress of the myocardium. However, in the two main variants we studied of adaptation-deadadaptation apparently this does not occur.

That fact that adaptation and deadaptation are mainly guaranteed by changes in the rate and amplitude of contraction corresponds to the conclusion that the cardiac muscle is determined by evolution towards the movement of changing volumes of blood, and not the development of a static force. Therefore, in the process of adaptation-deadadaptation there is a change precisely in the rate and amplitude of contraction-relaxation, while the changes in these parameters ensure changes in the final diastolic and systolic volumes in the heart. As a result the maximum attainable pump function of the heart during adaptation rises, and during deadadaptation drops. 176

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